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# Intercellular spiral waves of calcium in a two dimensional network of cells

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**Abstract** It is shown, by means of numerical simulations, that intercellular spiral waves of calcium can be initiated in a network of coupled cells as a result of a de-synchronization between  $Ca^{2+}$  oscillations in two domains. No artificial heterogeneities need to be imposed to the system for spontaneous formation of spiral waves. The de-synchronization occurs near the interface of the stimulated region (which acts as a pacemaker) and propagates over the entire network. We also find the outcome of the collision of two spiral waves.

**Keywords** Paracrine coupling · network of cells · Spiral waves ·  $Ca^{2+}$  oscillations

## 1 Introduction

Oscillations and waves of cytosolic calcium ( $Ca^{2+}$ ) have been reported in a large variety of cell types after stimulation by an extracellular agonist [1,2]. When stimulated, cells show a large variety of behaviour which has been observed in their cytoplasm, including pulsating pattern, plane and spiral waves. Various experimental and theoretical works have been carried out to uncover the mechanism underlying these oscillations [1,3,4,5]. In most models,  $Ca^{2+}$  oscillations are the result of the auto-catalytic regulation by a phenomenon called calcium induced calcium release (CICR) by which  $Ca^{2+}$  activates its own release from internal stores like endoplasmic reticulum.

Spiral waves have been initially observed in the cytoplasm of cells such as cardiac myocytes [6, 7], *Xenopus* Oocytes [8,9] and others [10,11]. In a general manner, cytosolic spiral waves have been identified as a characteristic behaviour of excitable media [12,13]. They can be initiated by spatial heterogeneity depending on the volume of the cell. That is in cardiac myocytes which are cells of small volume (1 mm in diameter vs. 100  $\mu m$  length) the presence of an unexcitable region created by

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nucleus [7] or by the existence of a region possessing a larger potentiality to release  $Ca^{2+}$  in *Xenopus* Oocytes (very large cells with a diameter of up to  $1000\ \mu m$ , much larger than myocytes [14]).

An important characteristic of  $Ca^{2+}$  oscillations is that  $Ca^{2+}$  signals can propagate from cell to cell. They have been observed not only to propagate between cells of the same type (homotypic  $Ca^{2+}$  waves) but also (at least in culture systems) between different cell types (heterotypic  $Ca^{2+}$  waves). For instance, intercellular  $Ca^{2+}$  waves have been observed propagating through ciliated tracheal epithelial cells [15,16], rat brain glial cells [17,18] and many other cell types [19,20]. Furthermore intercellular  $Ca^{2+}$  waves have been observed passing from glial cells to neurons and vice versa [21, 22]. For intercellular waves to propagate, two main types of coupling have been identified. The first mechanism involves the diffusion of a  $Ca^{2+}$  mobilizing messenger through gap junction [23] and the second relies on paracrine signalling [24] involving the release of a messenger in the extracellular space, binding to receptors on the neighbouring cells, and activation of cytosolic  $Ca^{2+}$  increase in target cells. A good review on calcium dynamics in general and on intracellular and intercellular waves in particular have been done recently by Dupont et al [25]. Particularly interesting are recent discoveries that intercellular waves are highly structured, with forms similar to the spatiotemporal organization of wave activity seen in *Xenopus* oocytes cytoplasm. In particular intercellular  $Ca^{2+}$  waves in hippocampal slices have recently been observed to form spontaneous spiral waves [26,27,28]. Numerical studies have been done to investigate how these spirals occur and how diverse parameter such as the intercellular conductance affects the process of spiral stability and breakup in an array of coupled excitable cells [28,29,30,31,32]. It is now clear that intercellular  $Ca^{2+}$  waves are a mechanism by which a group of cells can communicate with one another, and coordinate a multicellular response to a local event. Therefore, an understanding of the mechanisms underlying intercellular  $Ca^{2+}$  waves is of importance, not only for a general understanding of intercellular communication, but also for the understanding of a wide range of specific processes such as mucociliary clearance, wound healing, mechanical transduction, cell growth, information processing and others. For example, in the wound healing response, if a monolayer of epithelial cells is mechanically damaged the resultant intercellular  $Ca^{2+}$  wave sets up intercellular  $Ca^{2+}$  gradients which influence the initiation and direction of cell migration [19].

In this paper, our goal is to propose another mechanism by which intercellular spiral waves can be initiated. We use an existing minimal model to numerically investigate the occurrence and propagation of intercellular spiral waves of calcium. The paper is organized in the following manner. Section 2 presents the two-dimensional array of coupled cells while in section 3; we give the results of the numerical simulations. Conclusion is given in Section 4.

## 2 Model

To model intercellular calcium waves, two aspects must be considered: intracellular dynamics of calcium and coupling between cells. Two types of theoretical models have been developed so far: the spatiotemporal models and the temporal models. The spatiotemporal models take into account the fact that intracellular calcium waves are spatially distributed in cells. However in some cell types, with small diameter, such as hepatocytes ( $10\text{-}20\ \mu m$ ) [33,34] and pancreatic acinar cells ( $10\text{-}20\ \mu m$ ) [35], in which the intracellular propagation velocity is at the order of  $10\ \mu m.s^{-1}$  while intercellular speed is around  $120\ \mu m.s^{-1}$  [35], the spatial intracellular aspect can be neglected. Thus, the dynamics of the cells can be approximated by a set of ordinary differential equations. An interesting study by Tsaneva-Atanasova et al. [35] investigated in pancreatic acinar cells the temporal and the spatiotemporal models. Although the point-oscillator model can not explain all the phenomena exhibited in the cell networks such as synchrony, it has been found in Ref. [35] that it gives a reasonably accurate general picture when studying wave propagation. That is why we use the temporal model in this paper. However, to take into account the fact the signal wave takes a time to travel along a cell in some biological organs, we also carry out the numerical simulation of the model with a time delay added. This delay represents the time taken by a signal to propagate inside a cell before moving to the next cell. This constitutes a substitute or equivalent to the spatiotemporal model.

The model and numerical computations are based on the minimal model of Dupont et al [4] based on CICR that was originally designed to model intracellular  $Ca^{2+}$  oscillations in a cell and recently used to model intercellular propagation of  $Ca^{2+}$  waves in a 1D network of diffusively coupled cells [36].

A two-dimensional network of coupled cells is considered in this paper. As in Ref. [36], we assume that cells are coupled together by a bidirectional paracrine coupling. Let us consider  $x_{i,j}$  as the  $Ca^{2+}$  concentration in the cytosol and  $y_{i,j}$  the  $Ca^{2+}$  concentration in the internal store. Therefore, the cell defined by the  $i^{th}$  and  $j^{th}$  coordinates is described by the following set of equations (See Ref [36] for detailed on the modeling):

$$\frac{dx_{i,j}}{dt} = a_{i,j} - V_{2,i,j} + V_{3,i,j} + k_f y_{i,j} - k x_{i,j} + \beta_1 V_1 (x_{i+1,j} - 2x_{i,j} + x_{i-1,j}) + \beta_2 V_1 (x_{i,j+1} - 2x_{i,j} + x_{i,j-1}) \quad (1)$$

$$\frac{dy_{i,j}}{dt} = V_{2,i,j} - V_{3,i,j} - k_f y_{i,j} \quad (2)$$

with  $i = 0$  to  $N$  and  $j = 0$  to  $M$ . Node  $(i,j)$  indicates a different cell.

In these equations,

$$a_{i,j} = \begin{cases} V_0 + bV_1 & \text{if excited} \\ V_0 & \text{if not excited} \end{cases}$$

represents the term characterizing the excitation state of a cell.  $V_0$  represents a constant influx of  $Ca^{2+}$  from the extracellular media to the cytosol whereas  $bV_1$  represents an external excitation which can be due to a hormonal stimulus binding to receptors in the extracellular membrane of the cell. The binding to the receptors causes opening of ionic channels.  $\beta_1$  and  $\beta_2$  represent the coupling constant respectively in the  $x$  and in the  $y$  direction.

$$V_{2,i,j} = \frac{V_{m2} x_{i,j}^2}{k_2^2 + x_{i,j}^2}$$

represents the speed of  $Ca^{2+}$  pump from the cytosol to the internal store.

$$V_{3,i,j} = \frac{V_{m3} x_{i,j}^4 y_{i,j}^2}{(k_a^4 + x_{i,j}^4)(k_r^2 + y_{i,j}^2)}$$

represents the speed of  $Ca^{2+}$  liberation from the internal stores to the cytosol. The activation of this process is provoked by the  $Ca^{2+}$  itself characterizing the CICR process. The  $Ca^{2+}$  extrusion from the cytosol to the extracellular media is taken into account by the term  $kx_{i,j}$ . The  $Ca^{2+}$  can also pass from the internal stores to the cytosol via the passive flux given by the expression  $k_f y_{i,j}$ .

For the numerical simulation, no flux boundary conditions are used at the edge of the domain, defined as:

$$\begin{cases} x_{0,j} = x_{N+1,j} = 0 \\ x_{i,0} = x_{i,M+1} = 0 \end{cases} \quad (3)$$

We solve the model equations in an array of 50 by 50 cells shown in Fig. 1 (extension to larger arrays is used when necessary); parameters chosen for the simulation are listed in Table 1, they have been taken in Ref. [4]. The values of the coupling strength used in this work have been deduced from the study of Ref [36] and in a recent study by Gracheva and Gunton [37]. Equations (1) and (2) are extended later (in the next section) to include time delay representing the duration of signal propagation in a cell.

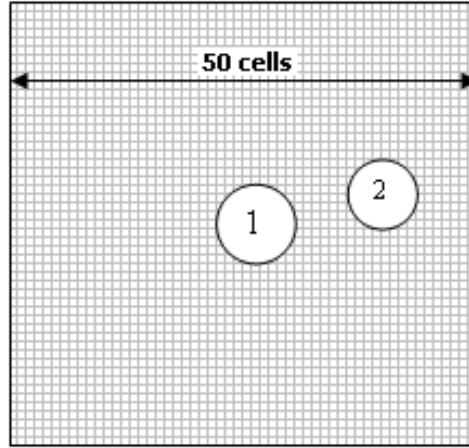
### 3 Results

We perform the numerical simulation by integrating the model equations together with the boundary conditions on a grid of 50 by 50 cells shown in Fig. 1. The fourth order Runge-Kutta algorithm is used with the time step equal to 0.001. For most results, a circular region with radius 5 cells is assumed to be stimulated at the center of the domain. This stimulated domain is defined as  $(i - i_0)^2 + (j - j_0)^2 = 5^2$ , where  $(i_0, j_0)$  is the coordinate of the cell at the center of the excited domain.

When the excitation act as a Dirac (for a localized mechanical or electrical excitation), the excited cells show a pick of calcium which can propagate to 2-4 neighbouring cells. However, when using a continued excitation to investigate spiral waves occurrence, one sees that when the degree of excitation is weak, a 1:1 locking is observed between cells of region 1 and region 2, therefore circular concentric

**Table 1** typical simulation constants for the minimal model

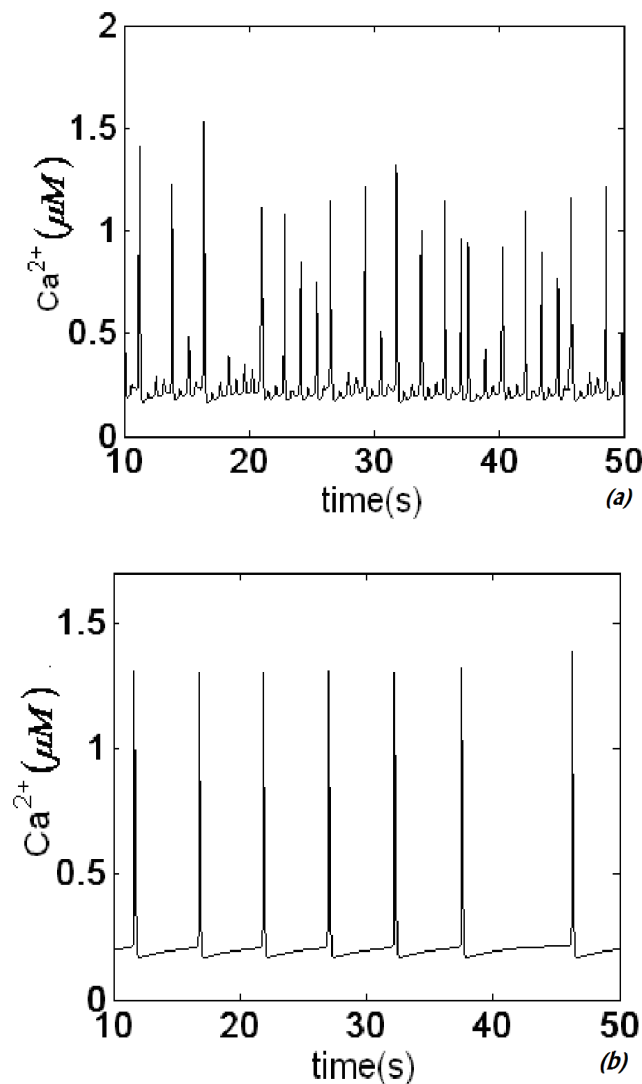
Parameter	Value
$k$	$2s^{-1}$
$k_f$	$1.0s^{-1}$
$k_2$	$1.0\mu M$
$k_a$	$0.9\mu M$
$k_r$	$2.0\mu M$
$V_0$	$1.3\mu M.s^{-1}$
$V_1$	$7.3\mu M.s^{-1}$
$V_{m2}$	$65.0\mu M.s^{-1}$
$V_{m3}$	$500.0\mu M.s^{-1}$
$\beta_1$	0.50
$\beta_2$	0.50



**Fig. 1** Typical geometry of system used to study intercellular spiral  $Ca^{2+}$  wave. Only two spatial dimensions are considered. Outer square represents a 50 by 50 cells. First inner circle (region 1) is region in which cells are stimulated. Second inner circle (region 2) is a small region in the non excited zone choose in other to observe the behaviour of non excited zone. In that frame, region 1 is a circular region of radius 5 cells.

waves are observed to propagate in the array. However, when the stimulation is strong, 1:1 locking is no more satisfied as seen in Fig. 2, where cells in the outer region of stimulation (region 2) exhibit weakly chaotic time behaviour, whereas cells in the stimulated region (region 1) show strong chaotic oscillations. Broad intercellular waterfronts with a width of 4-8 cells occur. These intercellular waves originate in the intermediate domain between the two regions and propagate in curvilinear and spiral patterns as shown in Fig. 3. Spiral waves are the result of waves de-synchronization between cells in the region 1 and region 2 which provoke a lateral instability at the intermediate area in between (which acts as a pacemaker).

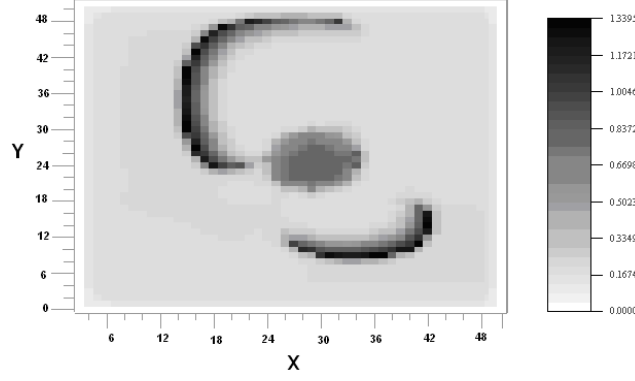
In a general manner,  $Ca^{2+}$  spiral waves occurrence does not depend on the shape and dimension of the stimulated region (region 1). However, when the dimension of the stimulated area decrease, one need to increase the coupling between cells in order to observe spiral occurrence. The numerical simulations also show that varying the area of the stimulated region can induce a change in the rotating direction of the spiral waves as shown in Figure 4. It is also observed that when the degree of excitation is further increased ( $b > 0.5$  for the same choice of parameters), it is possible to observe at different times, calcium puffs propagation (Fig. 5a), propagation of concentric waves (Fig. 5b) and spiral waves (Fig. 5c) which can suddenly occurs at a time further in the network. Calcium puffs are characterized



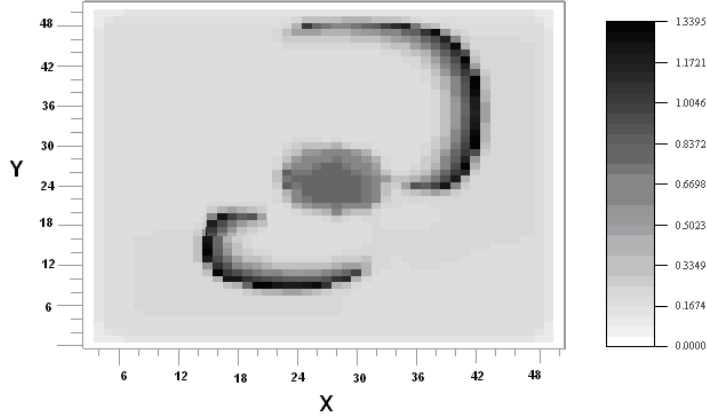
**Fig. 2** Calcium oscillations of a cell in: (a) the stimulated region (region 1), (b) the outer region of stimulation (region 2) with  $b = 0.5$ .

by small intercellular waves limited to 5-15 cells. The observation of the temporal behaviour of  $Ca^{2+}$  concentrations of cells shows that there is still chaotic evolution in the outer region of excitation whereas cells in the stimulated region shows a burst (Fig. 6) characterized by a higher pick of calcium and return to the equilibrium state.

Extending the array dimensions does not have an effect on the appearance of spiral waves. Considering for instance an array of  $80 \times 80$  cells, when stimulating another region of radius 5 centered at the cell ( $i = 75, j = 25$ ), one can see that when two curvilinear wavefronts collide, they annihilate at the point of contact. After collision, portions of the waves that have not collided merge and continue to propagate tangentially from the site of collision (Fig. 7). This behaviour is a standard property



**Fig. 3** Spiral  $Ca^{2+}$  waves propagating in the network for  $b = 0.50$ .

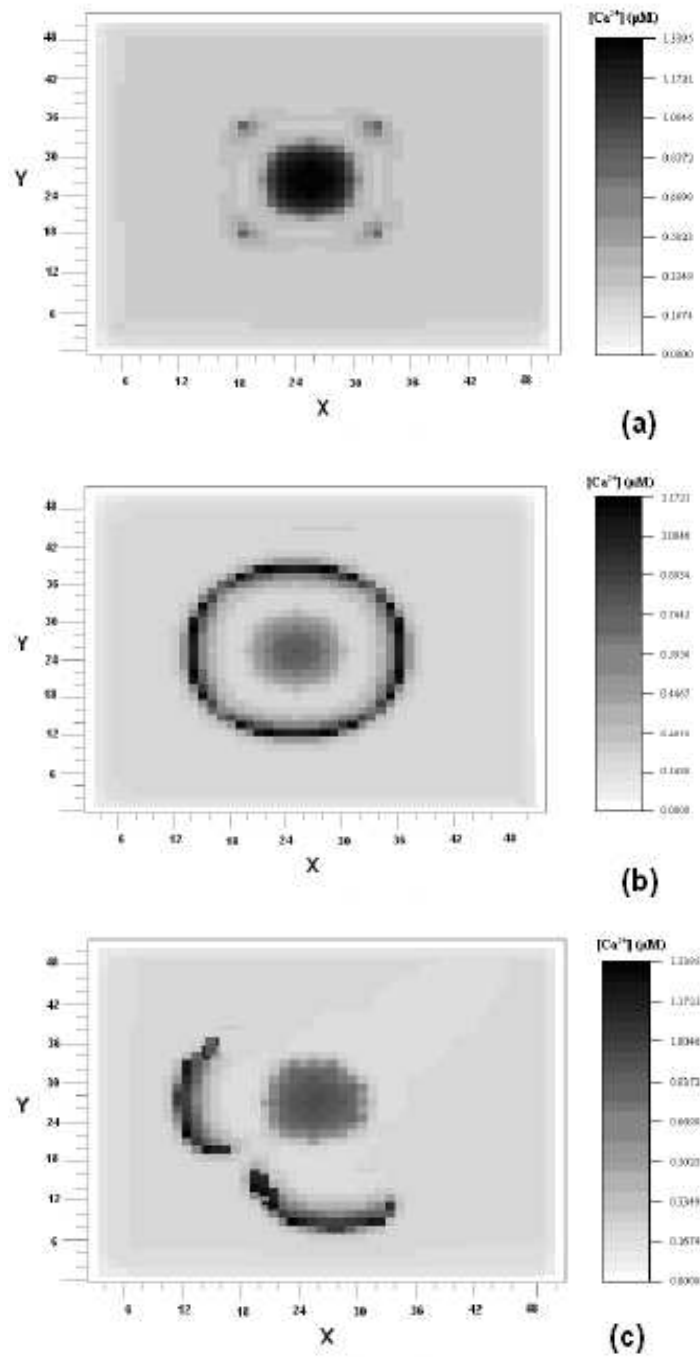


**Fig. 4** Spiral waves showing the change in the rotating direction of the spiral. Figure obtained for the same choice of parameter when stimulating a region of radius  $r = 3$  and  $b = 0.5$ .

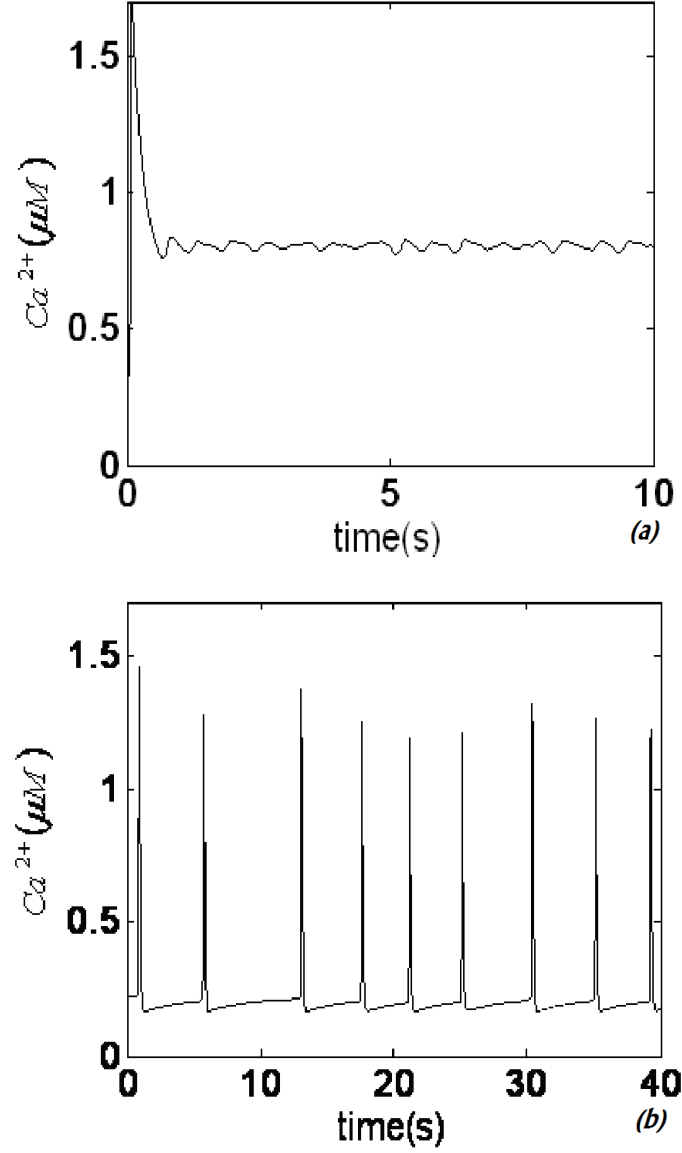
seen in excitable systems and which has already been reported experimentally in hippocampal slices cultures [26] and is a standard property of excitable media.

Since the calcium wave in some cell types propagate slowly, one needs to treat the cell as a spatially extended system in which the signal propagates from one side to the other. In order to take into account this fact without using partial differential equations, we introduce a time delay representing the duration of propagation of calcium wave in each cell. By so doing, the set of equations (1) and (2) becomes (we consider here the case where the wave propagates in only one direction):

$$\frac{dx_{ij}}{dt} = a_{ij} - V_{2,i,j} + V_{3,i,j} + k_f y_{i,j} - k x_{i,j} + \beta_1 V_1(x_{i-1,j}(t - \tau) - x_{ij}) + \beta_2 V_1(x_{i,j-1}(t - \tau) - x_{ij}) \quad (4)$$



**Fig. 5** Different patterns observed when the degree of excitation is high enough ( $b = 0.54$ ). (a) Calcium puffs propagation in the network obtained at  $t = 17.19s$ . (b) Concentric waves propagation obtained at  $t = 39.09s$ . (c) Spiral waves obtained at  $t = 58.07s$ .



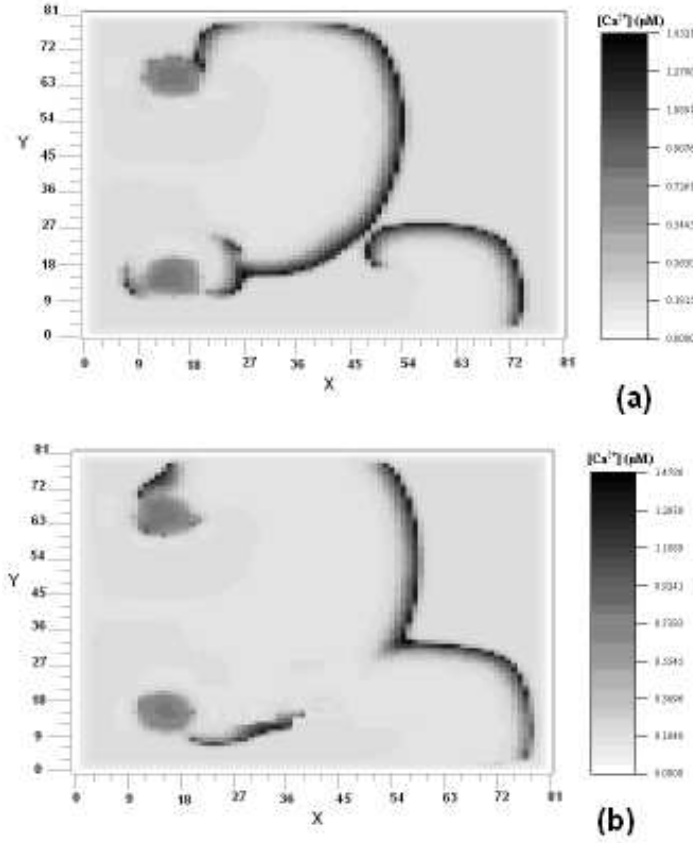
**Fig. 6** Calcium oscillations of a cell. (a) In the stimulated region where cells show a burst. (b) In the outer region of stimulation, cells show a chaotic behaviour for  $b = 0.56$ .

$$\frac{dy_{ij}}{dt} = V_{2,i,j} - V_{3,i,j} - k_f y_{i,j} \quad (5)$$

with  $i = 0$  to  $N$  and  $j = 0$  to  $M$ .

In this model,  $\tau$  is the time lapse necessary for the signal to propagate from one edge to the other of a cell. We consider in this case a unidirectional coupling. It is observed as shown in Fig. 8 that spiral still arise in the network, however, the de-synchronization occurred only in one side of the excited region. The effects of time delay on the speed of calcium wave have also been analyzed. To



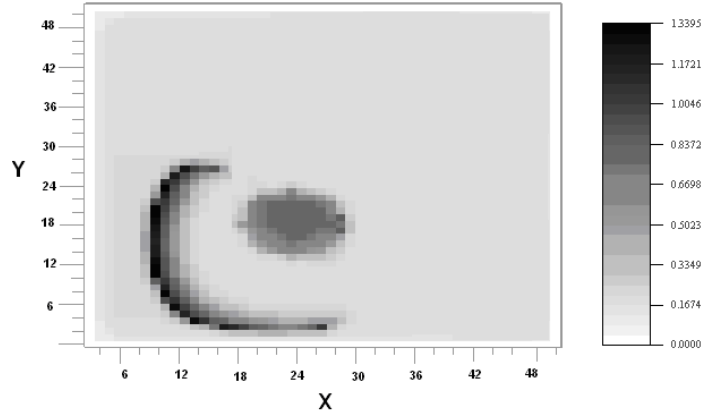


**Fig. 7** (a) Collision of two spiral waves in the array. (b) Annihilation and propagation of the portion of the waves that have not collided for  $b = 0.5$ .

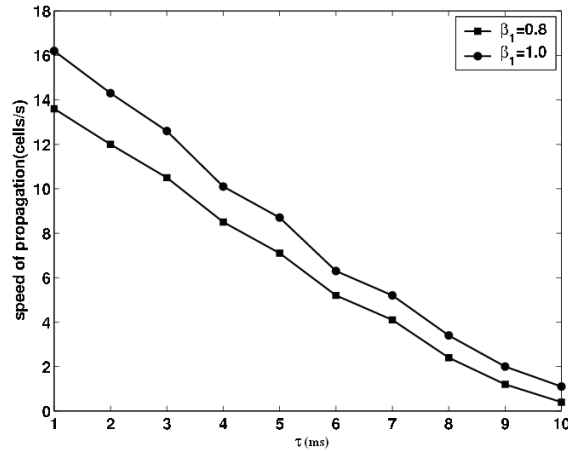
determine the speed of calcium signal propagating in the array, we look at the wave propagation along one direction and we take the times  $t_i$  and  $t_k$  when the signal arrives at two different sites  $i$  and  $k$  and the speed is the quantity  $k - i$  divided by  $t_k - t_i$ . Figure 9 shows that the speed of  $Ca^{2+}$  oscillations in the network decreases when the time lapse  $\tau$  increases and increases with the coupling coefficient  $\beta_1$ . This is understandable, since it is known that increasing the time lapse  $\tau$  implies that the signal takes more time to propagate across a cell.

#### 4 Conclusion

It is well known that a circular front that breaks in an asymmetric medium can initiate a spiral. This assumption has been used to show that intracellular spiral calcium waves can be initiated by an unexcitable region in cardiac myocytes[7] or an excitable region in *Xenopus* oocytes[14]. Also, it is known that intercellular spiral calcium wave can be initiated by simulating the release and propagation of inositol 1,4,5-trisphosphate in several homes in *Xenopus leavis*[27] or by the presence of a bolus (in the shape of a line) of  $Ca^{2+}$  which is placed directly behind the refractory region of a wave[28]. In addition to other studies aimed to investigate the origin of spiral calcium waves, in the present work, it is shown that intercellular spiral calcium wave can also be simply initiated in a network of coupled



**Fig. 8** Spiral waves observed when considering the delay between cells with  $b = 0.5$ .



**Fig. 9** Speed of propagation of  $Ca^{2+}$  waves obtained when varying the time lapse  $\beta_1 = 0.5$ ,  $\beta_2 = 0$  and  $b = 0.5$ .

cells as a result of the de-synchronization at the interface of an excited region and a non-excited region. Also, the outcome of the collision of two spiral waves has been found. This work complements a recent study using the spatiotemporal description of calcium flow and where it was found a mechanism of spiral generation at the interface between a pacemaker region and an outer region owing to the chaotic pulse transmission at the interface[38].

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